

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The study design, patient population, doses and drug exposures in the Phase 3 program were appropriate for the safety assessment of MP03-33 in patients 12 years of age and older. Children under the age of 12 years were not evaluated. Baseline demographics for patients in MP430 are presented in Table 6. Baseline characteristics and demographic information for patients in MP432 are presented in Table 8.

Table 8 Study MP432: Patient demographics and baseline characteristics				
Demographics	MP03-33 N=279	Astelin N=276	Total N=555	P
Age (years)				
Mean	40.8	40.8	40.8	0.979
SD	15.31	24.87	15.08	
Median	40.0	39.5	40.0	
Range	12-78	12-82	12-82	
12 to <18 [N(%)]	9 (3.2)	5 (1.8)	14 (2.5)	0.455
18 to <65 [N(%)]	248 (88.9)	253 (91.7)	501 (90.3)	
65 or older [N(%)]	22 (7.9)	18 (6.5)	40 (7.2)	
Sex				
Male	141 (50.5)	127 (46.0)	268 (48.3)	0.286
Female	138 (49.5)	149 (54.0)	287 (51.7)	
Race				
American Indian or Alaska Native	0	0	0	0.424
Asian	5 (1.8)	11 (4.0)	16 (2.9)	
Black	6 (2.2)	4 (1.4)	10 (1.8)	
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.2)	
White	264 (94.6)	257 (93.1)	521 (93.9)	
Other	3 (1.1)	4 (1.4)	7 (1.3)	
TNSS*				
Mean	9.64	10.00	9.82	0.270
SD	4.488	4.668	4.578	
Median	9.09	9.67	9.43	
Range	0.9-21.5	0.2-23.3	0.2-23.3	
Duration of rhinitis (years)				
Mean	11.0	12.1	11.5	0.134
SD	11.10	11.21	11.16	
Median	7.0	7.8	7.1	
Range	1-74	1-68	1-74	

\* Mean baseline reflective TNSS over 7-day lead-in period, including Day 1 AM.  
 Source: Volume 47, Section 11.2.1, Table 4

Overall, the patients in the long-term study tended to be slightly older with a shorter duration of allergic rhinitis symptoms and lower baseline TNSS scores. As the inclusion/exclusion criteria for the efficacy study were intended to identify patients with SAR symptoms of at least moderate severity, the discrepancy in baseline severity is expected.

The following tables detail the drug exposure of the patient population in Study MP430. Patient disposition is shown in Table 7. Table 10 presents the patient disposition for Study MP432. For Study MP432, the patient diaries indicated that 250 (89.6%) patients in the MP03-33 arm and 245 (88.8%) in the Astelin group had >75% compliance with study drug. The mean duration of exposure was 151.8 days for the MP03-33 group and 155.0 days for the Astelin group. The median duration was similar for both groups: 175.0 days for the MP03-33 arm and 174.0 days for the Astelin arm. Total number doses of taken was comparable as well: 273 doses for the MP03-33 group and 276 doses for the Astelin group. Four sprays (2 per each nostril) were counted as one dose.

Table 9 Study MP430: Duration of exposure and compliance							
	1 spray BID			2 sprays BID			Total (N=834)
	Astelin (N=137)	MP03-33 (N=139)	Placebo (N=137)	Astelin (N=137)	MP03-33 (N=146)	Placebo (N=138)	
<b>Duration (days)</b>							
N	137	138	136	137	146	137	831
Mean	14.5	14.6	14.4	14.6	14.4	14.3	14.5
SD	1.17	1.04	1.48	1.78	1.43	1.61	1.44
Median	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Range	10-18	11-18	7-17	1-19	7-17	6-18	1-19
<b>Total number of sprays</b>							
N	137	138	137	137	146	138	
Mean	57.1	57.6	56.4	110.2	108.5	108.0	
SD	11.49	11.68	11.79	16.35	12.88	15.00	
Median	56.0	56.0	56.0	112.0	112.0	112.0	
Range	22-112	28-128	26-124	4-152	52-132	48-136	
<b># patients ≥80% compliance [N(%)]</b>	135 (98.5)	137 (98.6)	135 (98.5)	132 (96.4)	143 (97.9)	133 (96.4)	815 (97.7)

Source: Vol 21, Section 14.1, Table 14.1.4

Table 10 Study MP432: Patient disposition			
Disposition	MP03-33 (N=281) N (%)	Astelin (N=278) N (%)	Total (N=559) N (%)
Randomized*	281 (100.0)	278 (100.0)	559 (100.0)
Completed 6 months	218 (77.6)	224 (80.6)	442 (79.1)
Discontinued	61 (21.7)	52 (18.7)	113 (20.2)
Adverse event	18 (6.4)	14 (5.0)	32 (5.7)
Treatment failure	15 (5.3)	17 (6.1)	32 (5.7)
Non-compliance	2 (0.7)	3 (1.1)	5 (0.9)
Withdrew consent	18 (6.4)	11 (4.0)	29 (5.2)
Lost to follow-up	3 (1.1)	4 (1.4)	7 (1.3)
Administrative problems	0	0	0
Other	5 (1.8)	3 (1.1)	8 (1.4)
<b>Total safety population</b>	<b>279 (99.3)</b>	<b>276 (99.3)</b>	<b>555 (99.3)</b>

\*Includes 7 patients who were randomized and do not have disposition data at 6 months; these patients are assumed to be ongoing in the study. Also includes 3 patients who were randomized to one treatment and incorrectly received the other treatment.

Source: Volume 47, Section 10.1, Table 3

### 7.2.2 Explorations for Dose Response

Formal exploration for dose response was not performed but was based on the approved doses for Astelin. In the Phase 3 program, both 1- and 2-spray doses were evaluated in the 2-week efficacy trial, MP430. The long-term safety study assessed only the higher 2-spray dose. However, both studies included Astelin as an active control, facilitating safety comparisons between MP03-33 and the existing safety database for both 1- and 2-spray Astelin.

### 7.2.3 Special Animal and/or In Vitro Testing

No special animal testing and/or in vitro testing studies were included in this application.

### 7.2.4 Routine Clinical Testing

Routine clinical testing was limited to prick-puncture allergen skin testing at screening, nasal exams, and vital sign measurements (weight, blood pressure, heart rate, and respiratory rate) in Study MP430. Blood laboratory testing was performed at the discretion of the investigator for individual cases if deemed appropriate. Given the pre-existing safety database for Astelin, the duration of the study, and the target population, limited clinical testing was appropriate. A full schedule of safety assessments is presented in Table 15.

In Study MP432, patients underwent standard hematology (complete blood cell count with white cell differential), chemistry (albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen, calcium, chloride, creatinine kinase, creatinine, glucose, AST, ALT, potassium, sodium, total protein, and uric acid), and urinalysis tests at Screening only. Screening 12-lead ECG was also performed at Screening. In addition, patients underwent periodic nasal exams exam and vital sign checks at Screening, Randomization, and Months 1, 3, and 6. Given the limited degree of systemic absorption and the existing safety database for Astelin, the routine clinical testing schedule was appropriate for the study. A full schedule of safety assessments is presented in Table 32.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Comparative pharmacokinetic evaluations between MP03-33 and Astelin are described in Section 4.4 Clinical Pharmacology, along with drug-drug interaction studies previously reviewed under NDA 20-114. No new in vitro or in vivo data on metabolism or clearance was submitted in this application.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Azelastine is currently the only approved antihistamine administered via intranasal inhalation. In addition to routine surveillance for adverse events, focused nasal exams were performed at regular intervals in Study MP430 and Study MP432 to assess local toxicities, such as mucosal erosion and septal perforation. Nasal exam findings were scored and analyzed separately in the individual study reports.

Given the extent of the pre-existing safety database available for Astelin, other special safety assessments were not indicated.

### **7.3 Major Safety Results**

#### **7.3.1 Deaths**

No deaths were reported in the clinical development program. No deaths are reported in the literature or postmarketing data provided.

#### **7.3.2 Nonfatal Serious Adverse Events**

No SAEs were reported in Study MP430. In Study MP432, 11 patients reported SAEs – 1 in the MP03-33 group and 11 in the Astelin group. One SAE in the MP03-33 group was a case of rectal bleeding related to rectal carcinoma that led to early discontinuation from the study. The other events in the MP03-33 treatment arm included the following: chest pain/angina pectoris, exacerbation of pain, basal cell carcinoma, cardiac pacemaker battery replacement, knee injury, salivary gland infection, and acute pyelonephritis. In the Astelin treatment arm, the SAEs included the following: calculus bladder, chlamydial pneumonia, syncope, prostate cancer, ovarian cyst, broken nose, foot fracture, spontaneous abortion, exertional dyspnea, and abdominal pain.

In the postmarketing database, one SAE was reported from France: a 58-year-old male diagnosed with angioimmunoblastic T-cell lymphoma, purpura, and thrombocytopenia.

There are no reports of death or SAEs associated with intranasal azelastine in the literature.

Based on the nature of the adverse events and the timing of drug administration, these SAEs do not appear to be related to intranasal azelastine use although a relationship cannot be conclusively ruled out on the basis of the information provided.

#### **7.3.3 Dropouts and/or Discontinuations**

In Study MP430, 2 patients randomized to receive MP03-33 discontinued prematurely due to adverse events, citing severe allergic conjunctivitis and heart palpitations, respectively. The former AE may have been a concomitant condition, since allergic rhinitis patients often also report eye allergy symptoms. The low frequency of heart palpitations in the safety database makes the relationship to treatment difficult to discern. However, this particular AE has been included in post-marketing spontaneous reports, and the terms “palpitations” and “atrial fibrillation” were recently added to the Astelin product label as a Changes Being Effected Special Supplement submitted on April 23, 2007.

In Study MP432, the types of adverse events cited as reasons for discontinuation were consistent with safety profile described in the Astelin product label. To date, 32 patients have withdrawn from the study due to a treatment-emergent AE. A wide range of adverse events were cited, although most of the terms were reported by no more than one patient. The following adverse events were cited by more than one individual in the MP03-33 group as a reason for discontinuation: rhinitis (n=2), headache (n=4), epistaxis (n=2), and nasal congestion (n=2). Patients could cite more than 1 AE if applicable.

#### 7.3.4 Significant Adverse Events

No other significant adverse events were reported.

#### 7.3.5 Submission Specific Primary Safety Concerns

Focused nasal exams were performed in the Phase 3 studies to assess local toxicities that may be associated with intranasal inhalation of MP03-33. The overall rate and severity of nasal irritation appeared comparable among MP033, Astelin, and placebo treatment groups.

In Study MP430, focused nasal exams were performed at Screening, Randomization, Day 7, and Day 14/Termination Day. No significant changes in the focused nasal exam were recorded in any of the treatment groups for the 14-day treatment period. The most common observations were physical findings consistent with allergic rhinitis (e.g. boggy turbinates, pale mucosa, watery mucosa, etc.)

In Study MP432, focused nasal exams were performed at Screening, Randomization, Months 1, 3, and 6. No nasal septal perforations were reported for either treatment groups. Other signs of nasal irritation were observed during focal nasal examinations as follows: epistaxis (3.6% in MP03-33 v. 5.1% in Astelin), pain (14.0% v. 14.5%, respectively), and ulceration (12.9% v. 11.9%, respectively). The two treatment groups appeared comparable in terms of these findings. Other aspects of the head and neck exam, e.g conjunctival injection, tympanic membrane erythema, lymphadenopathy, etc., were comparable as well.

### 7.4 Supportive Safety Results

#### 7.4.1 Common Adverse Events

The types of adverse events reported for MP03-33 in Study MP430 are consistent with the known safety profile of intranasal azelastine. MP03-33 compared favorably to Astelin in terms of dysgeusia. In general, the frequency of adverse events was lower than the rates observed in the controlled clinical trials supporting approval of Astelin 2 spray BID for treatment of SAR. For comparison, as noted in the Astelin product label, dysgeusia/bitter taste was reported in 19.7%, headache in 14.8%, somnolence in 11.5%, nasal burning in 4.1%, and epistaxis in 2.0%. For the Astelin 1 spray BID dosing regimen, dysgeusia was reported in 8.3% and somnolence in 0.4%. Common adverse events in Study MP430 are summarized in Table 11.

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 TRADENAME (Azelastine hydrochloride intranasal inhalation solution, 137 mcg)

**Table 11. Study MP430: Adverse events occurring in 2% or more of the safety population**

Preferred Term [N(%)]	1 Spray BID			2 Sprays BID			Total (N=835)
	Astelin (N=137)	MP03-33 (N=139)	Placebo (N=137)	Astelin (N=137)	MP03-33 (N=146)	Placebo (N=138)	
Any AE	37 (27.0)	29 (20.9)	22 (16.1)	34 (24.6)	41 (28.1)	27 (19.6)	190 (22.8)
Dysgeusia	13 (9.5)	8 (5.8)	2 (1.5)	11 (8.0)	10 (6.8)	3 (2.2)	47 (5.6)
Epistaxis	8 (5.8)	3 (2.2)	3 (2.2)	3 (2.2)	4 (2.7)	0 (0.0)	21 (2.5)
Headache	5 (3.6)	2 (1.4)	1 (0.7)	3 (2.2)	4 (2.7)	1 (0.7)	16 (1.9)
Nasal discomfort	3 (2.2)	0 (0.0)	1 (0.7)	6 (4.3)	2 (1.4)	0 (0.0)	12 (1.4)
Fatigue	1 (0.7)	0 (0.0)	1 (0.7)	3 (2.2)	3 (2.1)	1 (0.7)	9 (1.1)
Somnolence	2 (1.5)	2 (1.4)	0 (0.0)	2 (1.4)	3 (2.1)	0 (0.0)	9 (1.1)

Source: Vol 21, Section 12.2.2, Text Table 13

A similar safety profile was observed in the long-term study, MP432. Of note, dysgeusia was reported with similar frequency for MP03-33 and Astelin despite the use of taste-masking agents in MP03-33. There is a small discrepancy in the frequency of rhinitis reported between MP03-33 and Astelin, 3.6 versus 0.7%. This discrepancy is most likely incidental, although the possibility remains that the sweetened formulation may exacerbate rhinitis symptoms in patients with VMR, who are prone to non-allergic, sensorial triggers. The rate of rhinitis reported in the current product label for Astelin is 2.3%. Common adverse events in the long term safety study, Study MP432 are summarized in Table 12.

**Table 12. Study MP432: Adverse events occurring in ≥2% of patients in the MP03-33 treatment arm**

Adverse event	MP03-33 (N=279) N(%)	Astelin (N=276) N(%)
Any adverse event	139 (49.8)	132 (47.8)
Headache	25 (9.0)	22 (8.0)
Dysgeusia	23 (8.2)	23 (8.3)
Epistaxis	21 (7.5)	24 (8.7)
Nasopharyngitis	20 (7.2)	14 (5.1)
Viral infection	13 (4.7)	10 (3.6)
Pharyngolaryngeal pain	10 (3.6)	7 (2.5)
Cough	10 (3.6)	2 (0.7)
Rhinitis	10 (3.6)	2 (0.7)
Influenza	8 (2.9)	8 (2.9)
Bronchitis	8 (2.9)	6 (2.2)
Pharyngitis	8 (2.9)	5 (1.8)
Conjunctivitis	7 (2.5)	6 (2.2)
Nausea	7 (2.5)	6 (2.2)
Nasal mucosal disorder	7 (2.5)	5 (1.8)
Rhinalgia	7 (2.5)	5 (1.8)
Sneezing	7 (2.5)	4 (1.4)
Nasal discomfort	6 (2.2)	6 (2.2)
Upper respiratory tract infection	6 (2.2)	6 (2.2)

Source: Volume 47, Section 12.2.3.1, Table 8

The spontaneous post-marketing reports for Astelin are largely consistent with the safety profile demonstrated in these two studies, as well as the profile described in the current product label.

#### Less common adverse events

Given the relatively small sample size, less common adverse events from Study MP430 are included in Table 11 and are consistent with adverse events described in the current Astelin product label. In Study MP432, a range of adverse events were reported occurring at a frequency of <2% in 3 or fewer patients. Those adverse events included several events listed on the current product label, including somnolence (1.4%), nasal dryness (1.1%), and sinusitis (1.1%). A wide range of other events were reported but the relationship to treatment is difficult to assess due to the low numbers and the nature of the specific events. Additional details of these events are provided in the Section 10 Individual Study Reviews in the individual study reviews.

#### 7.4.2 Laboratory Findings

Laboratory testing performed in Studies MP430 and MP432 are described in Section 7.2.4. Unless otherwise indicated, laboratory testing was performed only at Screening in Study MP432 to establish a baseline. No routine follow-up assessments or formal analyses (e.g. measures of central tendency, outliers or shifts from normal to abnormal, or marker outliers and dropouts for laboratory abnormalities) were made.

#### 7.4.3 Vital Signs

##### Overview of vital signs testing

In Study MP430, vital signs were assessed at Screening, Randomization, Day 7, and Day 14 or the last day of the study. In Study MP432, vital signs were assessed at Screening (Day -7), Randomization, and Months 1, 3, 6, 9, and 12.

##### Analyses focused on measures of central tendencies

No clinically significant changes in mean and median values for systolic/diastolic blood pressure, pulse, respiratory rate, temperature, or body weight were observed during the 2-week treatment period in Study MP430 and over the first 6-month interval for Study MP432.

##### Analyses focused on outliers or shifts from normal to abnormal

The Applicant did not provide a formal analysis of shifts from normal to abnormal. Review of individual patient data listings did not reveal any clinically significant outliers or persistent changes in vital signs.

##### Marked outliers and dropouts for vital sign abnormalities

No marked outliers or dropouts for vital sign abnormalities were reported.

#### 7.4.4 Electrocardiograms (ECGs)

No thorough QT study was performed during the clinical development program. The submission does not include any formal analysis of ECG data or changes from baseline. In Study MP432, 12-lead ECGs were performed at screening only. ECGs were not performed in Study MP430.

Information on azelastine's effect on the QT interval is included in the current Astelin product label and is described in Section 4.4 Clinical Pharmacology.

#### 7.4.5 Special Safety Studies

No special safety studies were included in this submission.

#### 7.4.6 Immunogenicity

Not applicable.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

No formal dose exploration was performed in the clinical development program. Study MP430 included two different doses, 1 vs. 2 sprays BID, of MP03-33. Review of the adverse event frequency between these dose groups does not suggest a dose-dependence for the common adverse events reported, including dysgeusia, epistaxis, headache, nasal discomfort, fatigue, or somnolence.

#### 7.5.2 Time Dependency for Adverse Events

Comparison of the adverse event profiles for the 2-week study and the 6-month study do not suggest a time-dependency for the common adverse events reported for MP03-33. Nasal irritation is expected to be cumulative to some degree, although focused nasal exams over the 6-month study period in MP432 did not show any cases of significant mucosal erosion or septal perforation.

#### 7.5.3 Drug-Demographic Interactions

There are no clear patient-predictive factors such as age, sex, gender, or race for the common adverse events reported. In general, elderly patients appear to be more likely to experience sedation secondary to antihistamines, and the proposed product label includes a recommendation for conservative dosing in elderly patients. However, the small number of patients over the age of 65 in both Study MP430 and Study MP432 limits this type of subgroup analysis for adverse events occurring at such low frequencies.

#### 7.5.4 Drug-Disease Interactions

No apparent interactions between MP03-33 and allergic rhinitis and concomitant therapies were identified. Theoretically, nasal discomfort and epistaxis may be increased in patients also using intranasal corticosteroids for the treatment of SAR. However, intranasal corticosteroids were not

permitted during the studies, so no formal assessment of this potential interaction was made made.

#### 7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were included in this submission. The current product label for Astelin states that concomitant use of azelastine with alcohol or other CNS depressants should be avoided due to additional reductions in alertness and additional impairment of CNS performance may occur. Cimetidine (400 mg twice daily) has been shown to increase the mean Cmax and AUC of orally administered azelastine by 65%. Ketoconazole interferes with the measurement of plasma concentrations of azelastine but does not appear to cause any clinically relevant effects. Concomitant administration of theophylline with oral azelastine does not cause any drug-drug interactions.

### 7.6 Additional Safety Explorations

#### 7.6.1 Human Carcinogenicity

No formal carcinogenicity studies with MP03-33 have been conducted. The adverse event profile for MP03-33 does not suggest a carcinogenic effect. Preclinical studies performed with oral azelastine did not demonstrate a tumorigenic effect. These studies were previously reviewed under NDA 20-114.

#### 7.6.2 Human Reproduction and Pregnancy Data

No data on MP03-33 and human pregnancy is available. Information in the current product label for Astelin notes that azelastine is rated as Pregnancy Category C.

#### 7.6.3 Pediatrics and Effect on Growth

The NDA provides evidence of safety and efficacy of MP03-33 in patients 12 years of age and older. The safety and efficacy of Astelin in patients 5 to 11 years of age has been shown in previous controlled clinical trials reviewed under NDA 20-114, \_\_\_\_\_

\_\_\_\_\_. Although efficacy of MP03-33 in this age group can be extrapolated from the data for Astelin as well as adult efficacy data, \_\_\_\_\_

\_\_\_\_\_. As a result, the recommendation of the clinical review is an age range restricted to patients 12 years of age and older.

The safety and effectiveness of both the sweetened and unsweetened formulations has not been established in patients under the age of 5 years. As part of a post-marketing commitment and to satisfy PREA, the Applicant intends to study intranasal azelastine in children ages 2 to 5 years. Studies in children under the age of 2 have been waived, as the existence of SAR in this age group is not established.

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No formal growth effect studies in children have been conducted with intranasal azelastine.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdosages have been reported to intranasal azelastine. Due to the route of administration, overdose is unlikely to result in clinically significant adverse events, with the exception of potential increase in somnolence. Azelastine is not expected to have drug abuse potential, or cause withdrawal or rebound effects.

#### 7.7 Additional Submissions

The Applicant submitted a 4-month safety update, dated December 13, 2007. The update included information on the ongoing long-term safety study, MP432, as well post-marketing spontaneous adverse events and literature reports covering June 1, 2007 through November 30, 2007. The information in the update has been incorporated in the discussion of safety in this review.

### 8 Postmarketing Experience

The Applicant has submitted a summary of the postmarketing experience covering the time period from December 13, 2005 to November 30, 2007. Data since initial approval up to December 13, 2005 was previously reviewed as part of Supplement 014 to NDA 20-114, approved on February 17, 2006. The data was presented as report frequencies using MedDRA preferred terms, along with case narratives for SAEs. The information is incorporated into Section 7 of this review.

### 9 Appendices

#### 9.1 Literature Review/References

The Applicant has provided results of a search of the scientific literature and noted 3 clinical studies in reference to intranasal azelastine from the time period of December 13, 2005 to November 30, 2007. A PubMed search performed by the reviewer [search term: azelastine; limits: human, clinical trial, meta-analysis, randomized clinical trial] yielded 131 references, including the 3 submitted by the Applicant. A brief review of these reports was performed. No new safety signals were identified from these reports.

#### 9.2 Labeling Recommendations

At the time of this review, labeling discussions are ongoing. Major labeling recommendations include the following: